Docket No.: 9189 (A-947C)
01017/40451C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,791 Art Unit: 1644

Filed: May 19, 1995 Examiner: R. Schwadron

For: HUMAN TNF RECEPTOR

DECLARATION OF STEWART LYMAN, PH.D. UNDER 37 C.F.R 1.132

1. I received a Ph.D. in Oncology from the McArdle Laboratory for Cancer Research at the University of Wisconsin-Madison in 1984. I did postdoctoral research at the Fred Hutchinson Cancer Research Center in Seattle, and joined Immunex Corporation as a molecular biologist in 1988. I was a scientist at Immunex Corporation for 14 years, eventually becoming Director of Extramural Research. After Amgen acquired Immunex in 2002, I stayed on and worked for Amgen for three months in a transitional role. Since 2004, I have managed my own consulting business, and I am being compensated for my time consulting on this matter at my usual hourly rate. I also own 100 shares of Amgen stock. My Curriculum Vitae is attached as Exhibit A.

2. I have reviewed the above-identified application as originally filed. I have been informed that the effective filing date of the above-identified application is August 31, 1990. In particular I have reviewed page 9, line 19 to page 10, line 10 of the application, which refers to Smith *et al, Science* 248: 1019-1023, 1990 (referred to hereafter as "Smith (1990)"):

EXHIBIT B

> In addition thereto, the present invention is also concerned with DNA sequences coding for proteins and soluble or non-soluble fragments thereof, which bind TNF. Thereunder there are to be understood, for example, DNA sequences coding for non-soluble proteins or soluble as well as non-soluble fragments thereof, which bind TNF, such DNA sequences being selected from the following:
>
> (a) DNA sequences as given Figure 1 or Figure 4 as well as their complementary strands, or those which include these sequences;
>
> (b) DNA sequences which hybridize with sequences defined under (a) or fragments thereof;
>
> (c) DNA sequences which, because of the degeneracy of the genetic code, do not hybridize with sequences as defined under (a) and (b), but which code for polypeptides having exactly the same amino acid sequence.
>
> That is to say, the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP [TNF binding proteins]. One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990).

3. I have been informed that the Patent Office has objected to the amendment to the specification which inserts the phrase "incorporated by reference" with respect to the sequence provided in Smith (1990), because this insertion introduces new matter into the application. I have reviewed page 2 of the Office Action dated June 8, 2010 which sets out this objection and make this declaration to address the objection.

4. I have been informed that the standard for properly incorporating material by reference into a patent application is that the application clearly identifies the reference publication and the application must clearly convey an intent to incorporate the material by reference.

5. I believe that I am qualified by my education and training to attest to what one skilled in the art would have understood from reading the application as of August 31, 1990. In 1990, I was well experienced in the molecular biology of type I transmembrane receptors. For example, we had recently cloned and expressed the c-kit tyrosine kinase receptor protein, a type I transmembrane receptor (Williams et al., Cell, 63, 167-174,1990). In addition, I had worked on elucidating the relationship between the IL-4 receptor (also a type I transmembrane receptor) and other cytokine receptors. (Cosman et al., Trends in Biol. Sci. 15:265-270, 1990) The extracellular, ligand-binding domain of the IL-4 receptor showed homology to several other cytokine receptors. This homology allowed us to define a new class of cytokine receptors. Starting in 1988, I also initiated a project at Immunex that resulted in the cloning of a number of cell surface receptors and their ligands. During the course of this work, I had occasion to make DNA constructs encoding soluble forms of type I transmembrane receptors (i.e., not membrane bound) as well as insoluble chimeric receptors containing the extracellular domain of one receptor fused to the transmembrane and cytoplasmic domains of a different receptor.

6. I note the following points as background to the discussion below. I read the application as being concerned with two tumor necrosis factor binding proteins ("TNF-BP"), one about 55 kD in size and one about 75 kD in size. The application's discussion of these two TNF binding proteins is consistent with what was known in the art as of August 31, 1990, i.e. that there were two membrane bound TNF receptors (TNFR) of approximately these sizes. The former is also

variously referenced in the literature as TNFR I, 55 kd TNFR, or p55 TNFR. The latter is also variously referenced in the literature as TNFR II, 75 kd TNFR, or p80 TNFR.

7. Figure 4 of the application displays a partial nucleotide and amino acid sequence corresponding to the p75 TNFR.

8. There is a description in the application of the specific full length sequence of the 75 kD TNFR. It is clear from the citation to the Smith (1990) article at page 10, lines 9-10 of the application that the Applicants knew of the Smith (1990) article when they drafted the application and intended to refer to its sequence.

9. It is disclosed in the application (page 35, lines 22-33) that Figure 4 is a partial cDNA sequence. Since the amino acid sequence of Figure 4 is almost identical (almost 99% identical) to that of Smith (1990), it would be clear to one of skill in the art that the sequence of Figure 4 was a partial sequence of the same protein described in Smith (1990). Attached as Exhibit B is an alignment of the Figure 4 sequence with part of the Smith (1990) sequence of p75 TNFR to illustrate this point. Further, the disclosure (page 33, lines 7-19) of the following 18-mer as the amino terminal peptide of a protein detected as a 65/75 kD band was also consistent with this conclusion because the 18-mer matches exactly the mature amino terminus of p75 as disclosed in Smith (1990), save for one amino acid, the identity of which was not determined:

Leu-Pro-Ala-Gln-Val-Ala-Phe-X-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys.

10. When the entirety of the quote in paragraph 2 above is read, one sees that the paragraph refers to soluble and non-soluble fragments of TNF binding proteins,

i.e. the TNF receptors described in the application. Thus, one of skill in the art would have concluded that the citation to Smith (1990) was a reference to whatever soluble or non-soluble fragments of TNF binding proteins were described in the article. Despite differences between the sequences disclosed in the application and those in the Smith (1990) article, the amino acid sequences are nearly 99% identical overall. I would interpret the quote in paragraph 2 above to mean that the Smith sequence was contemplated by the inventors because the Smith (1990) article is specifically cited.

11. One of skill in the art would not have read the application by itself without reference to any other known information. Instead, such a person would have read the application in view of what was known in the art at the effective filing date, particularly in view of the following statements in the application:

> "the present invention embraces . . . One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990)."

Specification, page 10, lines 3-10. One of skill in the art would also have noted that Dembic *et al. Cytokine* 2(4): 231-7, 1990, published by the same authors as the inventors on the application, disclosed the entire sequence of the mature 75 kD TNFR, which was the same sequence as in Smith (1990), and the same extracellular region (page 232 to page 233, upper left column; and Figure 1 at page 232). Thus, one of skill in the art would have had no doubt that the inventors were in possession of the entire p75 sequence as of August 31, 1990 and that the Applicants clearly intended to incorporate the entire p75 amino acid sequence into the specification.

12. For all of these reasons, it is clearly indicated in the specification that the skilled artisan should look to the Smith (1990) article as a source of information about sequences of soluble fragments of the TNF-BP that can be used.

13. The citation includes the journal name, journal volume, page numbers and year, and thus is a complete citation that uniquely identifies the article. Figure 3 of Smith (1990) discloses the only TNF receptor sequence in this publication, from among the p55 or p75 TNF receptors that are the subject of the application. Thus, the application clearly identifies the reference publication and the application clearly conveys an intent to incorporate by reference the sequences in Smith (1990) of soluble or non-soluble TNF receptors.

14. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Dated: Sept. 3, 2010 Stewart Seyman

EXHIBIT A

CURRICULUM VITAE

NAME: Stewart David Lyman

PRESENT POSITION: Manager, Lyman BioPharma Consulting LLC

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PLACE OF BIRTH: New Rochelle, NY

EDUCATION:

Degree	Institution	Discipline
B.S. (Magna cum laude)	State University of New York at Albany, Albany, NY	Biology
Ph.D.	McArdle Laboratory for Cancer Research University of Wisconsin Madison, WI	Oncology
Dissertation:	"Genetic and Metabolic Factors that May Affect the Biological Activity of Xenobiotics in Mice"	

EMPLOYMENT HISTORY:
2003 – present: Manager, Lyman BioPharma Consulting LLC

1988-2002: Immunex Corporation:
- 1999-2002: Director, Extramural Research
- 1993-1999: Senior Staff Scientist
- 1988-1992: Staff Scientist
  - Project Chair, creator of the Receptors in Search of Ligands (RISOL) Project, 1989-1994. Receptors used as tools to clone novel ligands.
  - Project Chair of the Signal Transduction Project, 1990-1991.
  - Project Chair of the Flt3 Ligand Development Project, 1994-1996.
  - Project Co-Chair of the Expressed Sequence Tag Project, 1995-1996.
  - Project Co-Chair of the Core Pipeline Technology Project, 1997-1999.
  - Project Co-Chair of the Basic Biology Project, 1999.

1984-1988: Post-doctoral Fellow: Fred Hutchinson Cancer Research Center, Seattle, WA. Laboratory of Dr. Larry Rohrschneider. Studied the mechanism of cellular transformation by the v-*fms* oncogene.

PROFESSIONAL ASSOCIATIONS:

American Association for the Advancement of Science

RESEARCH INTERESTS:

Identification of novel growth factors; role of growth factors in development of the hematopoietic and immune systems, role of growth factors in oncology.

HONORS AND AWARDS:

Regents Scholarship, SUNY Albany, 1973-1977
Biological Honor Society, SUNY Albany, 1976-1977
Danforth Fellowship nominee, SUNY Albany, 1977
U.S. Public Health Service National Research Service Award
McArdle Laboratory for Cancer Research, 1977-1982
NIH Postdoctoral Training Grant in Viral Oncology
University of Washington, January-September 1985
Individual National Research Service Award,
National Cancer Institute, October 1985-December, 1987.
Visiting Scientist Fellowship, Molecular Biology Computer Research
Resource, Dana-Farber Cancer Institute, Boston, MA; December 1986

ADVISORY BOARDS:

Advisory Board Member "Modern Drug Discovery", 1998 - 2004.

AWARDED PATENTS AND PATENT APPLICATION FILINGS:

U.S. Patent #5,512,457 – Cytokine designated Elk ligand
U.S. Patent #5,627,267 – Cytokine designated Elk ligand
U.S. Patent #5,670,625 – Elk ligand fusion proteins
U.S. Patent #5,728,813 – Antibodies directed against Elk ligand
U.S. Patent #5,554,512 – Ligands for Flt3 receptors
U.S. Patent #5,843,423 – Flt3 ligand stimulation of hematopoietic cells
U.S. Patent #6,190,655 – Flt3 ligand uses for exogenous gene transfer
U.S. Patent #6,540,992 – Methods for using elk-L to enhance neuronal survival
U.S. Patent #6,555,520 – Human TSLP DNA and polypeptides
U.S. Patent #6,630,143 – Antibodies against flt3 ligand
U.S. Patent #6,632,424 – Human flt3 ligand
U.S. Patent #6,762,030 – Ligand for CD7, and methods for use thereof
U.S. Patent #6,919,206 – Medium containing flt3 ligand for culturing hematopoietic cells
U.S. Patent #6,994,989 – FLK-1 binding proteins
U.S. Patent #7,041,282 – Ligands for flt3 receptors
U.S. Patent #7,045,128 – Antibodies against flt3 ligand

WO 92/00376 – The c-*kit* ligand (Steel factor)
WO 97/17442 – Novel VEGF related ligand for flk-1/KDR receptor

WO 99/33984 – V197 Polypeptide
WO 99/33983 – V201 Polypeptide
WO 99/33877 – V196 Polypeptide

INVITED TALKS AT MEETINGS:

Biology of IL-4 Receptor:
FASEB conference on Receptors, June 1990
Biotechnological Applications in the 1990's, UC-Irvine, Irvine, CA, May 1990

Biology of Steel Factor (c-*kit* Ligand):
Armand Hammer Workshop: Regulation of Hematopoietic Stem Cells, La Jolla, CA, October 1990

Nargis Dutt Memorial Symposium: Cytokines in Clinical Medicine, UC-Irvine, Irvine CA October 1990

Stromal Regulation of Hematopoiesis, Bethesda, MD, June 1991
Blood Cell Growth Factors Meeting, Beijing, China, August 1991
American Society for Pediatric Hematology/Oncology, Chicago IL, September 1991
AACR 43rd Annual Symposium on Fundamental Cancer Research: "Growth Factors and their Receptors in Cancer: Basic Mechanisms and Therapy" Houston, Texas, November 1991

Biology of Flt3 Ligand:
Plenary Session, 1993 ASH meeting, St. Louis, MO. December, 1993
Keystone Hematopoiesis Conference, Breckenridge, CO January, 1994
Advances in Bone Marrow Transplantation, Valhalla, NY March 7, 1994
Advances in Hematopoiesis Conference, Tokyo, Japan July 1994
The Metcalf Forum: Polyfunctionality of Hematopoietic Regulators, Dublin, Ireland September 1994

Mehdi Tavissoli Memorial Symposium: Hematopoietic Stem Cells, Reno, Nevada, November 1994
Taniguchi Foundation Symposium: Regulation of Hematopoietic Stem Cells, Osaka, Japan, December 1994
9th Symposium, Molecular Biology of Hematopoiesis, Genoa, Italy, June 24-27, 1995
International Society for Experimental Hematology, Dusseldorf, Germany, August 26-31, 1995
International Symposium on Bone Marrow Transplantation: Basic and Clinical Studies, Tokyo, Japan, October 9-10, 1995
American Association for Cancer Research Satellite Symposium: Cytokines and Cytokine Receptors, Lake George, NY, October 1995
Southern Blood Club, New Orleans, LA, February 1, 1996
Wilsede Conference, Human Leukemia Meeting, Hamburg, Germany, June 14-18, 1996
Research Trends in Hematopoietic Cell Culture, Tokyo, Japan, August 26-28, 1996
Biological Therapy of Cancer, Munich, Germany, June 11-14, 1997
IBC conference "Hematopoietic Stem Cells" San Diego, CA, June 23-24, 1997
International Society for Experimental Hematology, Cannes, France, August 24-28, 1997
Mini-symposium: Tyrosine kinase receptors, University of Lund, Sweden, August 29, 1997

PUBLICATIONS (Abstracts not included):

1. **Lyman, S.D.**, Poland, A., and Taylor, B.A. Genetic polymorphism of microsomal epoxide hydrolase activity in the mouse. J. Biol. Chem. 255, 8650-8654, 1980.

2. **Lyman, S.D.**, and Poland, A. Effect of the brachymorphic trait in mice on xenobiotic sulfate ester formation. Biochem. Pharm. 32, 3345-3350, 1983.

3. Jordan, V.C., Bain, R.R., **Lyman, S.D.**, and Brown, R.R. Analysis of Tamoxifen and its metabolites. In: Drug Determination in Therapeutic and Forensic Context, Ed. by E. Reid and I.D. Wilson, Plenum Press, p. 219-225, 1984.

4. **Lyman, S.D.**, and Jordan, V.C. Antiestrogenic effect of trifluoperazine in mice. Biochem. Pharmacol. 34, 2221-2224, 1985.

5. **Lyman, S.D.**, and Jordan, V.C. Metabolism of Tamoxifen and its uterotrophic activity. Biochem. Pharmacol. 34, 2787-2794, 1985.

6. **Lyman, S.D.**, and Jordan, V.C. Possible mechanisms for the agonist actions of Tamoxifen and the antagonist actions of MER-25 (Ethamoxytriphetol) in the mouse uterus. Biochem. Pharmacol. 34, 2795-2806, 1985.

7. Jordan, V.C., Tate, A.C., **Lyman, S.D.**, Gosden, B., Wolf, M.F., Bain, R.R., and Welshons, W.V. Rat uterine growth and induction of progesterone receptor without estrogen receptor translocation. Endocrinology 116, 1845-1857, 1985.

8. **Lyman, S.D.**, and Jordan, V.C. Metabolism of non-steroidal antiestrogens, In: Estrogen and Antiestrogen Action (V.C. Jordan, Ed.), University of Wisconsin Press, Madison, WI, pp. 191-219, 1986.

9. **Lyman, S.D.**, and Rohrschneider, L.R. Analysis of functional domains of the v-*fms* encoded protein of feline sarcoma virus by linker insertion mutagenesis. Molecular and Cellular Biology 7, 3287-3296, 1987.

10. **Lyman,S.D.**, Park,L. and Rohrschneider, L.R. Colony stimulating factor-1 induced growth stimulation of v-*fms* transformed fibroblasts. Oncogene 3, 391-395,1988.

11. **Lyman, S.D.** and Rohrschneider, L.R. The kinase activity of the v-*fms* encoded protein has a low pH optimum. Oncogene Research 4, 149-155, 1989.

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14. Cosman, D., **Lyman, S.D.**, Idzerda, R.L., Beckmann, M.P., Park, L.S., Goodwin, R.G., and March, C.J. A new cytokine receptor superfamily. Trends in Biol. Sci. 15: 265-270, 1990.

15. Williams, D. E., Eisenman, J. , Baird, A. , Rauch, C. , Van Ness, K., March, C.J., Park, L.S., Martin, U., Mochizuki, D.Y., Boswell, H. S., Burgess, G. S., Cosman, D., and **Lyman, S.D.** Identification of a ligand for the c-*kit* proto-oncogene. Cell, 63, 167-174, 1990.

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20. Brannan, C.I., **Lyman, S.D.**, Williams, D.E., Eisenman, J., Anderson, D.M., Cosman, D., Bedell, M. A., Jenkins, N. A., and Copeland, N. G. Steel-Dickie mutation encodes c-*kit* ligand lacking transmembrane and cytoplasmic domains. Proc. Natl. Acad. Sci. 88, 4671-4674, 1991.

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26. Williams, D.E., Anderson, D.M., and **Lyman, S.D.** Identification and characterization of a ligand for the c-*kit* proto-oncogene. The Regulation of Hemoglobin Swithching. Proceedings of the 7th Meeting on Hemoglobin Switching. G. Stamatoyannopoulos and A. Nienhuis, Eds. Johns Hopkins University Press, Baltimore, MD. pp. 454-459, 1991.

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33. Dolci, S., Williams, D.E., Ernst, M. K., Resnick, J. L., Brannan, C.I., Lock, L.F., **Lyman, S.D.**, Boswell, H. S. and Donovan, P. J. Requirement for mast cell growth factor for primordial germ cell survival in culture. Nature 352, 809-911, 1991.

34. **Lyman, S. D.** and Williams, D. E. Alternate splicing of mRNAs that encode mast cell growth factor and the c-*kit* proto-oncogene: Potential effects on protein interactions, pp. 183-193, in Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Martin Murphy, Jr., (Ed.), Alpha Med Press , Dayton, OH 1991.

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46. Hu, Q., Trevisan, M., Xu, Y., Dong, W., Berger, S., **Lyman, S.D.**, Williams, D.E., and Minden, M.D.. The effect of murine c-kit on the leukaemogenic potential of 32D cells. J. Clin. Invest. 95, 2530-2538, 1995.

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EXHIBIT B

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GAP of: p75-P20333  check: 5724  from: 1  to: 461

p75(smith)

 to: p75-EP939121  check: 2507  from: 1  to: 392

p75(EP939121)

 Symbol comparison table: /apps/gcg/gcgcore/data/rundata/blosum62.cmp
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     Length Weight:      2   Average Mismatch: -2.248

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             Ratio:  5.235              Gaps:      1
 Percent Similarity: 98.977   Percent Identity: 98.977

       Match display thresholds for the alignment(s):
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            .         .         .         .         .
301 phlpadkargtqgpeqqhllitapsssssslessasaldrraptrnqpqa 350
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231 PHLPADKARGTQGPEQQHLLITAPSSSSSSLESSASALDRRAPTRNQPQA 280
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351 pgveasgagearastgss.dsspgghgtqvnvtcivnvcsssdhssqcss 399
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281 PGVEASGAGEARASTGSSADSSPGGHGTQVNVTCIVNVCSSSDHSSQCSS 330
            .         .         .         .         .
400 qasstmgdtdsspsespkdeqvpfskeecafrsqletpetllgsteekpl 449
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331 QASSTMGDTDSSPSESPKDEQVPFSKEECAFRSQLETPETLLGSTEEKPL 380
            .
450 plgvpdagmkps 461
    ||||||||||||
381 PLGVPDAGMKPS 392
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